EDITORIAL COMMENTARY

Terra Incognito: The Ureter in Urinary Tract Infection

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(See the major article by Floyd et al, on pages 1589–96.)

Knowledge characterizing the cause and evolution of acute uncomplicated urinary infection has greatly expanded [1]. Women and girls who experience this syndrome have a familial propensity for infection that is determined, at least in part, by a modified innate immune response caused by genetic variation [2]. This propensity influences not only when infection occurs, but also clinical presentations such as whether infection is symptomatic or asymptomatic, or presents as pyelonephritis rather than being limited to the bladder. For instance, selected polymorphisms that reduce Toll-like receptor-4 function are associated with asymptomatic bacteriuria [2, 3], and genotypic variants of 1RF3, a transcription factor, and CXCR1, an IL-8 receptor, are associated with an increased familial incidence of pyelonephritis [2, 4]. Selected behavioral factors, particularly sexual intercourse or spermicide use in young, sexually active women, also increase the frequency of infection in women at risk.

Infection is also contingent upon the complex interaction of virulence characteristics of *Escherichia coli* and the host innate immune response. *E. coli* are isolated from 80%–95% of episodes of acute uncomplicated urinary tract infection, and these strains comprise a subset of *E. coli* referred to as uropathogenic *E. coli* (UPEC). UPEC strains are characterized by an array of virulence factors that influence the persistence and localization of bacteria in the urinary tract, as well as the intensity of the immune response [5]. These virulence factors include fimbriae, flagella, diverse other adhesins, siderophores, toxins, polysaccharide capsules, and additional properties that facilitate the avoidance of host defenses, injury of host cells, or stimulation of the inflammatory response. A mannose-sensitive type I pilus adhesin, FimH, is universal in UPEC strains and essential for cystitis to be established [5]. In pyelonephritis, a class II PapG mannose-resistant adhesin of the P fimbrial family is associated with 80% or more of pyelonephritis strains, but is uncommon in strains from infections presenting as asymptomatic bacteriuria or acute cystitis [5, 6].

Absent from this crowded landscape is the ureter. Investigations that characterize the pathogenesis of uncomplicated urinary infection present the kidney and bladder largely in isolation, whereas they are clearly an anatomic and physiologic continuum linked by the ureter. There is no syndrome of ureteritis, and this clinical silence may partially explain the apparent neglect of the ureter in studies of urinary infection. For many patients with complicated urinary tract infection, likely including pregnant women, the progress of organisms from the bladder to the kidney seems a straightforward mechanical event when reflux of urine from the bladder into the ureter accompanies the genitourinary abnormality. But reflux is not characteristic of acute uncomplicated urinary tract infection, where the genitourinary tract is normal by definition. The ureter in this syndrome cannot simply function as an inert hollow tube, but must be permissive for bacteria to ascend from the bladder to the kidneys so that pyelonephritis develops. Progression to pyelonephritis is very infrequent in women who present with acute cystitis, so the ureter must, in most cases, maintain an effective barrier. What mechanisms allow bacteria and infection to subvert ureteric defenses and permit bacteria to reach the kidney?

In this issue of The Journal, Floyd et al [7] report a series of investigations characterizing the impact of *E. coli* on ureteric contractility. Ureteric peristalsis is an important function for limiting bacterial ascent. A diverse library of well characterized *E. coli* strains were assayed in an ex vivo female rat ureter model. The *E. coli* strains included several UPEC originating from distinct, clinically important clonal groups, an avian pathogenic *E. coli*, enteropathogenic *E. coli*, and non-UPEC commensal strains. The participation of 1 important virulence factor, FimH, in mediating contractility...
changes was described using mannose inhibition studies, and the strain-specific prevalence of mannose-sensitive adhesins for all UPEC strains correlated with the extent of ureteric contractility change. Deletion mutants of the fimH gene and fim operon of 1 UPEC strain were also created and tested to further characterize the potential role of FimH.

The results of these investigations provide some insights that are potentially relevant to the pathogenesis of pyelonephritis. All UPEC strains decreased ureteric contractility, but the effect among strains was highly variable, ranging from 9.5%–96.7%. None of the non-UPEC strains altered contractility. The UTI89 strain possessed the greatest effect in decreasing ureteric contractility, but this effect was virtually abolished following mannose inhibition. The fim mutants of UTI89 also had no effect on ureteric contractility, while inhibition was restored to approximately 45% when the fimH deletion strain was complemented with wild-type fimH.

These observations suggest that depressed ureteric contractility is a consistent attribute of UPEC, although the degree of impact varies among strains, and the changes may be mediated by FimH. Clearly, this suggests a potential mechanism to allow E. coli to travel up the ureter from the bladder to the kidneys. The type 1 pilus observations, however, were not consistent for all UPEC strains. Only 3 of the 4 UPEC strains that showed moderate or high inhibition of contractility had their inhibitory effect blocked by mannose. The EC958 strain showed no change in contractility following inhibition by mannose. This strain was 1 of 2 ST 131 strains, an important global clone that causes acute, uncomplicated urinary infection. The UPEC strains with the greatest contractility impairment generally had the highest type I fimbriae titers. The EC958 strain, however, had 78% inhibition of ureteric contractility but only a moderate to low prevalence of type I fimbriae. Thus, UPEC characteristics beyond FimH will need to be explored to fully explain the inhibition of ureter contractility.

Once a role for the ureter is acknowledged, additional questions immediately come to mind regarding the function of the ureter in limiting access to the kidney and mechanisms that modify this function. Does the strain-specific relative impairment of contractility correlate with the likelihood of pyelonephritis? What influence does the class II PapG pilus have on contractility or other ureter functions, given the strong association of this adhesin with the clinical presentation of pyelonephritis? What other E. coli virulence characteristics modify ureter function, and what alterations other than contractility will impede ureter functions to limit bacterial ascension? What about other pathogens important in acute, uncomplicated urinary infection? Staphylococcus saprophyticus is isolated from 5%–15% of acute cystitis episodes. It is isolated from symptomatic cystitis but is an uncommon cause of acute pyelonephritis [8]. Could a differential effect in modifying ureter peristalsis explain the relatively lower likelihood of isolating this organism in cases of pyelonephritis as compared to UPEC? Moreover, the studies reported here used rat tissue for the contractility assay. Will these observations be consistent in studies that use human ureter tissue, and if so, is there a genetic variation?

Impaired ureteric contractility in the presence of UPEC was recognized over 40 years ago. Several early studies characterizing ureter function were reported during the many urinary tract infection investigations that occurred after the quantitative urine culture was standardized for microbiologic diagnosis of urinary tract infection in the late 1950s. Using an in vivo female dog model, Grana et al [9] reported in 1968 that direct installation of 10^7 bacteria/mL into the mid-ureter precipitated immediate defective peristalsis and stasis of urine flow, and these effects continued as long as the urine remained infected. The effect on peristalsis was similar for E. coli or Pseudomonas aeruginosa, but Proteus mirabilis installation did not eliminate ureteral peristalsis. In the study’s histopathological assessment, E. coli infection was associated with mucosal ulceration and extensive denudation of the epithelium. The effects on peristalsis and histology were similar when E. coli endotoxin alone was infused, rather than live organisms. Inflammation in the ureter was also observed for P. aeruginosa and P. mirabilis, but the histologic patterns differed. At the same time, Teague and Boyarsky [9] reported that temporary suppression of ureteral activity was consistently observed in an in vivo dog model following retrograde injection of live or dead E. coli or E. coli endotoxin. The effect was immediate, and it was concluded that this occurrence was evidence for a direct effect on the ureter, rather than being secondary to established infection. These intriguing studies provide valuable information that can be used to elucidate the role of the ureter in the pathogenesis of pyelonephritis. The older observations are consistent with the present study in demonstrating a marked effect of E. coli on ureteric contractility, but in a different mammalian species and in an in vivo model. The observations that endotoxin alone has effects similar to live organisms and evidence for direct infection of the ureter raise additional mechanistic possibilities.

The studies of Floyd et al return us to an appreciation of the ureter as an anatomic imperative for the development of pyelonephritis in women with acute, uncomplicated urinary infection. The consistent observation of decreased ureteric contractility following exposure to UPEC strains, but not with non-UPEC strains, is remarkable. The mechanism through which this modification occurs requires further elucidation and study of a broader array of strains. Recognition of a role for the ureter adds an additional level of complexity to the interplay of variables
imposed by the host and organism that ultimately leads to the clinical presentation of acute, uncomplicated pyelonephritis.

**Note**

*Potential conflicts of interest.* The author certifies no potential conflicts of interest.

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**References**